REMARKS

Claims 1-18 were pending. Claims 4 and 16 are cancelled herein and no new claims are added. Thus, after entry of this amendment, **claims 1-3, 5-15, 17 and 18 will be pending**. Of these, claims 5-12 are currently withdrawn.

Claim 1 is amended to incorporate the limitations of claim 4. No new matter is introduced by this amendment.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office does not address how claim 1 lacks compliance with the written description requirement, therefore Applicants understand this rejection applies only to claim 16. Solely in an effort to advance prosecution of this application, claim 16 is cancelled herein, rendering the rejection moot.

PRIORITY

In the non-final Office action mailed March 17, 2010, the Office indicated that the pending claims were only entitled to a priority date of October 4, 2006, the "filing" date of the instant application. In response, Applicants pointed out that the current application is the U.S. National Phase of PCT Application No. PCT/US2004/22232, filed July 9, 2004, and therefore contains the identical disclosure as the PCT application. Thus, the pending claims are entitled to a priority date at least as of July 9, 2004. Applicants further argued that the pending claims are adequately supported by both priority provisional applications, U.S. Application No. 60/485,959, filed July 9, 2003, and U.S. Application No. 60/511,244, filed October 14, 2003. Applicants maintain that all pending claims are supported by the original disclosures of both provisional applications and are therefore entitled to a priority date of July 9, 2003.

Although not explicitly stated in the current Office action, it appears that the Office has granted a priority date at least as of July 9, 2004 to each of the pending claims. In reference to the priority provisional applications, the Office indicates on page 5 of the current Office action that "Applicant is not entitled to the priority date in these application[s] for all claims in the instant claim set because the information contained within the previous referred filings does not support the granting of an earlier filing date." The Office further states on page 6 of the current

action that the provisional applications "do not seem to define what is meant by non-acidified sodium nitrite." Since it is not clear what priority date(s) has been granted to each claim, Applicants request that the Office explicitly state this information in the next Office communication.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-3 and 13-18 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Webb *et al.* (*Br. J. Pharmacol.* 138 (Proceedings Supplement):20P, April 2003), Goldfrank *et al.* (Goldfrank's Toxicological Emergencies, 7th Edition, 2002, page 1511) and Remington's Pharmaceutical Sciences (pages 420-425, 1980). **Claims 1-3 and 13-18** are also rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Shaw *et al.* (U.S Patent No. 4,650,484) and Goldfrank *et al.*

Claim 1 is amended herein to incorporate the limitations of claim 4, which is not rejected in view of the above combinations of cited references. Claims 2, 3, 13-15, 17 and 18 depend directly or indirectly from, and thus incorporate all limitations of, claim 1. Claim 16 is cancelled herein. Accordingly, both of the above rejections under 35 U.S.C. § 103(a) are now moot.

Claim 4 is rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Shaw *et al.*, Goldfrank *et al.* and Modin *et al.* (*Acta. Physiol. Scand.* 171:9-16, 2001), or alternatively, in view of Webb *et al.*, Goldfrank *et al.*, Remington's Pharmaceutical Sciences and Modin *et al.* Claim 1 is amended herein to incorporate the limitations of claim 4 (*i.e.* to specify that sodium nitrite is administered to a circulating concentration of about 0.6 to 240 μM). Claims 4 and 16 are cancelled. Accordingly, Applicants traverse this rejection as it applies to amended claim1 and dependent claims 2, 3, 13-15, 17 and 18.

Applicants note that the Office does not specifically address the combination of Webb *et al.*, Goldfrank *et al.*, Remington's Pharmaceutical Sciences and Modin *et al.* The arguments presented by the Office on pages 10-14 of the current Office action appear to focus solely on the combination of Shaw *et al.*, Goldfrank *et al.* and Modin *et al.* Thus, in the arguments presented below, Applicants do not specifically address the combined teachings of Webb *et al.*, Goldfrank *et al.*, Remington's Pharmaceutical Sciences and Modin *et al.* However, Applicants believe the arguments presented below are relevant to both rejections. In particular, Applicants assert that

the discussion below of the deficiencies of Modin *et al.* clearly demonstrate that the combination of Webb *et al.*, Goldfrank *et al.*, Remington's Pharmaceutical Sciences and Modin *et al.* fails to render the pending claims obvious.

The Office has failed to establish a *prima facie* case of obviousness

Applicants submit that the combination of Shaw *et al.*, Goldfrank *et al.* and Modin *et al.* does not teach each and every element of the pending claims. Thus, the Office has failed to establish a *prima facie* case of obviousness against the pending claims. None of the cited references teach or even suggest that *non-acidified* nitrite is a vasodilator *in vivo*, or more particularly, that administration of non-acidified sodium nitrite decreases blood pressure and/or increases vasodilation in a subject.

Moreover, the combination of cited references does not teach or suggest administering non-acidified nitrite to achieve a circulating concentration of 0.6 to 240 μM, as recited in amended claim 1. Although Shaw *et al.* list sodium nitrite as a potential vasodilator, this reference provides no guidance on what a therapeutically effective amount of sodium nitrite would be to increase vasodilation or decrease blood pressure, and more particularly does not teach a circulating concentration of 0.6 to 240 μM. Similarly, Goldfrank *et al.* do not provide any teachings related to sodium nitrite doses or circulating concentrations. The Office alleges that Modin *et al.* cure this deficiency by teaching a threshold relaxatory effect of sodium nitrite at 10 μM and relaxation to near basal tone at 1000 μM. The Office further alleges that Modin *et al.* teach that human plasma has 0.45 μM nitrite and human serum has 6.6 μM nitrite and it would have been obvious to administer nitrite in an amount that would increase the plasma and serum concentrations of nitrite, and that it would have been merely routine to optimize the amount of nitrite administered to a subject.

However, Applicants point out that one of ordinary skill in the art reading Modin *et al.* would not have had any motivation to optimize *non-acidified* nitrite to decrease blood pressure and/or increase vasodilation because Modin *et al.* clearly teaches that **acidified** nitrite is a significantly better vasodilator. Furthermore, as discussed in more detail below, Modin *et al.* employ an *in vitro* system that is not representative of the *in vivo* effects that occur in the presence of circulating blood. Thus, the dose used by Modin *et al.* in their *in vitro* system does not provide adequate guidance on an appropriate, therapeutically effective dose of non-acidified

nitrite to administer to a subject and certainly does not teach the use of a circulating concentration of 0.6 to 240 μM of sodium nitrite *in vivo*.

The deficiencies of Modin *et al.*

As previously discussed in the Amendment and Response filed March 26, 2010, the aortic ring bioassays taught by Modin *et al.* are not representative of the *in vivo* effects of sodium nitrite on vasodilation, primarily because these assays were carried out in the absence of blood.

One significant difference between the claimed subject matter and the teachings of the cited art is that the studies of Modin *et al.* were conducted in aortic ring bioassays **without circulating blood**, in contrast to Applicants' claimed method, which specifically recite that the non-acidified sodium nitrite contacts blood in the subject. The Modin *et al.* studies are qualitatively not different from similar work performed by Robert Furchgott in 1952 (Furchgott & Bhadrakom, *J. Pharmacol. Exp. Ther.* 108(2):129-43, 1953; of record). These experiments were all performed in **isolated** aortic rings **without blood in them**. Because these studies required non-physiological conditions – extremely low oxygen tension and low pH, as well as high nitrite concentrations – they were not considered by those of skill in the art to reflect what would happen in the human circulation (that is, in the presence of blood).

Thus, there would be no reasonable expectation that sodium nitrite as employed in Modin *et al.* would predictably function in the methods provided in Shaw *et al.* – that is, there was no reasonable expectation that sodium nitrite would work *in vivo* in the presence of blood. This was clearly evinced by the Lauer *et al.* paper (*Proc. Natl. Acad. Sci. USA* 98:12814-12819, 2001; of record)) – which concluded that "nitrite lacks intrinsic vasodilator action." One of skill in the art, prior to Applicants' invention, would have expected that the presence of blood would have **inhibited** the NO generated from nitrite, not increased it.

It was shown by Isbell *et al.* (*Am. J. Physiol. Heart Circ. Physiol.* 293(4):H2565-72, 2007; of record) that oxygenated blood inhibits the nitrite induced vasodilation of aortic rings. Thus, it is very clear that the results of *in vitro*, blood-free experiments such as described in Modin *et al.* **are not applicable to an *in vivo* situation**.

Moreover, paragraph 4 of the Kelm Declaration, paragraph 5 of the Ignarro Declaration and paragraph 3 of the Lundberg Declaration (each of which was submitted with Applicants' response filed October 13, 2009) specifically discuss the deficiencies of the *in vitro* system

described by Modin *et al.* In particular, the Kelm Declaration states that the model used by Modin *et al.* is a poor model because "the regulatory factors present in blood that play a physiological role in the vasodilation process are absent...*Of particular importance is the lack of blood in the aortic ring preparations*." It should be noted that Dr. Lundberg was the senior author of the Modin *et al.* paper and he asserts that because the published assays were performed in the absence of blood, the findings "were not considered predictive of whether or not similar concentrations of inorganic nitrite would cause vasodilation under non-acidic/non-hypoxic physiological conditions *in vivo*" (see paragraph 3 of the Lundberg Declaration). Thus, even the senior author of the Modin *et al.* manuscript does not believe his own earlier study (Modin *et al.*) was predictive of Applicants' presently claimed subject matter.

In response to Applicants' arguments, the Office points to MPEP 7.16(c)III and *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), which establish that in order to determine the probative value of an expert opinion, the Examiner must consider (i) the nature of the matter sought to be established; (ii) the strength of any opposing evidence; (iii) the interest of the expert in the outcome of the case; and (iv) the presence or absence of factual support for the expert's opinion. It appears the Office attempts to rebut Applicants' arguments by addressing one of these considerations (the strength of any opposing evidence) by citing four references (U.S. Patent No. 6,153,186; U.S. Patent No. 5,436,271; U.S. Patent No. 6,110,453; and Gladwin *et al.*, *Free Radic Biol Med* 36(6):707-717, 2004) that teach the use of aortic ring bioassays. The Office alleges that these references teach that results obtained using aortic ring bioassays are the same results found in an *in vivo* setting. Applicants strongly disagree.

Submitted herewith is a Declaration under 37 C.F.R. § 1.132, signed by Dr. Mark T. Gladwin, a co-inventor of the application. As stated in paragraphs 3-4 of the Declaration, the aortic ring bioassays of Modin *et al.* were conducted in the absence of red blood cells and hemoglobin, both of which inhibit vasodilation induced by nitric oxide (NO) and acetylcholine. Due to the known inhibitory effect of red blood cells and hemoglobin on NO-induced vasodilation (see Exhibit B; Fujiwara *et al.*, *J Neurosurg* 64:445-452, 1986, a copy of which is submitted in an IDS herewith; and Ignarro *et al.*, *Proc Natl Acad Aci USA* 84:9265-9269, 1987, of record), one of skill in the art would have expected that in an *in vivo* setting, where both red blood cells and hemoglobin are present, nitrite would have decreased potency relative to the

potency of nitrite in an aortic ring bioassay performed in the absence of red blood cells and hemoglobin. Thus, one of skill in the art would not have expected that the results obtained using an aortic ring bioassay in the absence of red blood cells and hemoglobin (as was done by Modin *et al.*) to measure the vasodilatory activity of nitrite would be representative of the results obtained *in vivo*. Instead, one of skill in the art would have expected that the concentration of nitrite required to induce vasodilation *in vivo* would have been greater than the concentration required to achieve the same effect in the aortic ring bioassay.

Dr. Gladwin states in paragraph 6 of the Declaration that none of the four references cited by the Office describe experiments that provide any teachings related to comparing *in vitro* (aortic ring bioassay) and *in vivo* vasodilatory concentrations of nitrite or NO. In fact, three of the cited references (Gladwin *et al.*, U.S. Patent No. 5,463,271 and U.S. Patent No. 6,110,453) do not provide any comparison between an *in vitro* aortic ring assay and an *in vivo* system for the particular studies being described. Accordingly, based upon the cited references, as well as the prior art as a whole as of the priority date of the current application, one of skill in the art would not have concluded that the concentration of sodium nitrite identified by Modin *et al.* as inducing relaxation of the aortic segment in an aortic ring bioassay would be the same concentration of sodium nitrite that causes vasodilation *in vivo*.

It should be further noted that the experts that have submitted Declarations for the present application (Drs. Louis Ignarro, Bruce Freeman, Malte Kelm, Jon Lundberg and S. Bruce King), have no financial or commercial interest in the outcome of this case. In fact, in some instances, the Declarants are research competitors of the present inventors. Furthermore, in one instance, the findings disclosed in the current application contradict an earlier study of one of the Declarants (Dr. Malte Kelm). Moreover, each of the expert Declarants have provided more than ample support for their opinions, such as by citing other publications that were known in the field as of the priority date of the current application, or by discussing their own work (for example, Dr. Jon Lundberg, the lead author of Modin *et al.*, discusses his opinion on what his own work does and does not teach). Applicants request that the Office consider these other factors when weighing the value of the Declarations submitted during prosecution of this application.

Summary

The combination of cited references does not teach that *non-acidified* nitrite is a vasodilator *in vivo* and further does not teach *a circulating concentration of 0.6 to 240 μM* of *non-acidified sodium nitrite* to administer to a subject in order to decrease blood pressure and/or increase vasodilation. Moreover, based on the prior art as a whole, one of skill in the art would not have expected that non-acidified sodium nitrite would have vasodilatory activity at a circulating concentration of 0.6 to 240 μM. Accordingly, the Office has failed to establish a *prima facie* case of obviousness.

DOUBLE PATENTING REJECTION

Claims 1-4 and 13-18 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1-4, 10 and 14-18 of co-pending Application No. 12/748,184. Applicants request that this rejection be held in abeyance until claims from one or both of the applications have been allowed.

REQUEST FOR EXAMINER INTERVIEW AND CONCLUDING STATEMENT

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and allowance of the claims is respectfully requested. If any issues remain, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office Action in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Jodi L. Connolly/
Jodi L. Connolly, Ph.D.
Registration No. 54,044

cc: Docketing